REMARKS

Claims 1, 4-5 and 7-13 are currently pending in the application. Claim 3 has been canceled as being drawn to a non-elected invention. Applicants reserve the right to pursue the claims as originally filed is this or a separate application(s).

Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of the previous rejections under 35 U.S.C. §112, first paragraph for lack of written description and enablement.

Rejections under 35 U.S.C. §103(a)

The rejection of claims 1, 4, 5 and 7-12 as being obvious over Co, *et al.* (US 2002/0176855 A1) in view of DeBoer, *et al.* (US Patent No. 5,747,034), Cottens, *et al.*, (WO 95/16691), and Strom, *et al.*, (Therapeutic Immunology, Austen *et al.*, (Ed.) Blackwell Science, Cambridge, MA 1996) has been maintained. More specifically, the Office Action states:

> The primary and secondary references provide clear teachings of combining immunosuppressives in therapeutic regimens to inhibit the immune response including antibodies and rapamycin . . . . . Therefore, the prior art provides motivation and expectation of success in combining immunosuppressives in therapeutic regimens including the expected advantage of additive-synergistic effects and reducing toxicity of certain immunosuppressives.

Applicants respectfully traverse this rejection. Co *et al.* teach methods of inhibiting the B7:CD28/CTLA-4 pathway. Specifically, they teach that immune-related or autoimmune diseases and disorders can be treated using an antibody specific to B7-2, and that treatment of these diseases may be facilitated by co-administration of an anti B7-2 antibody with an anti B7-1 antibody, or antibodies to the corresponding receptors, CD28 and CTLA-4. Co *et a.,* further teach that methods of treatment also involve co-administration of a humanized anti B7-2 antibody ***or*** a humanized anti B7-1 antibody with other standard therapy drugs (see page 10, column 2). Therefore, despite the assertions in the Office Action, Co *et al.* do not teach or suggest that methods of treating any immune disease or disorder with a combination of an anti B7-1 antibody, an anti B7-

2 antibody ***and*** rapamycin as presently claimed. In fact, nothing in the teachings of Co *et al.* even suggests that one should administer these three molecules, let alone provides any evidence whatsoever that the co-administration of this combination could be advantageous. Moreover, Co *et al.* do not teach, or even suggest, that rapamycin should be considered a "standard therapy drug." Indeed, the very absence of rapamycin in the list of examples provided by Co, *et al.* clearly implies that, as experts in the field, they did not even consider using rapamycin in combination with one B7 antibody, let alone two B7 antibodies as presently claimed.

DeBoer *et al.* disclose the combination of anti-B7-1 antibodies and cyclosporine results in tolerance, which was a surprising discovery since it had been previously suggested that cyclosporine *inhibited* anergy induction (column 5, eighth paragraph). DeBoer *et al.* teach that co-administration of a B7-1 antibody with cyclosporine A "completely blocks" T cell activation (column 25, second paragraph). DeBoer *et al.* further state that

> Given that both B7-1 and B7-2 may provide the co-stimulatory signal to T cells for the production of IL-2 (a molecule that inactivates anergy genes), ***it is surprising that blocking only B7-1 in combination with cyclosporine results in T cell tolerance***. This may be explained by the fact that signal transduction after cross-linking with CD28 results in two independent signaling pathways, one being Cyclosporine-sensitive and one being Cyclosporine-insensitive. It may be that ***signal transduction after interaction of CD28 with B7-2 is mediated by the Cyclosporine-sensitive pathway***. (column 6, lines 27-33). (emphasis added).

Thus, Applicants respectfully submit that one of ordinary skill in the art would conclude from the teachings of DeBoer *et al.* that the combination of anti B7-1 antibodies and cyclosporine would be equivalent to the combination of anti B7-1 and anti B7-2 antibodies because cyclosporine acts as a *substitute* for anti B7-2 antibodies. Moreover, while DeBoer *et al.* suggest that other immunosuppressive agents, including rapamycin, might be used in combination with B7-1 antibodies, they fail to provide any teaching whatsoever that any of these other immunosuppressive agents would be as effective as cyclosporine, let alone suggest the co-administration of rapamycin with two anti B7 antibodies as presently claimed.

Accordingly, even when the teachings of Co *et al.* and DeBoer *et al.* are combined they merely teach that immune disorders can be treated by inhibiting the B7 pathway using one of the following combinations (1) anti B7-1 and antiB7-2 antibodies; (2) anti B7-2 antibodies and standard therapy drugs; or (3) anti B7-1 and cyclosporine (as a substitute for anti B7-2). Indeed, one of ordinary skill in the art, when presented with the combined teachings of DeBoer *et al.* and/or Co *et al.* in their entirety would not have been able to motivated to use a combination of anti-B7-1 antibodies, anti B7-2 antibodies and rapamycin to treat an immune disorder. Nor would they have been able to reasonably predict that this combination would result in an increased level of survival in a clinically relevant animal model when compared to the level of survival in animals treated only with B7-1 and B7-2 antibodies as demonstrated by Applicants (see Examples 2 and 3 and Figure 4).

The teachings of Cottens *et al.* and Strom *et al.* do not cure the deficiencies of Co *et al.* and DeBoer *et al.* Cottons *et al.* merely teach novel rapamycin derivatives that have "an improved pharmacological profile over rapamycin, exhibit greater stability and bioavailability, allow for greater ease in producing formulations, and are more potent immunosuppressants" (page 2, second paragraph). Cottens *et al.* generally suggest that the novel compounds of the invention might be used in combination with other immunosuppressive drugs or immunosuppressive monoclonal antibodies, but provide no teaching that any combination is effective in inducing anergy. Strom *et al.* generally teach a multi-tiered approach to immunosuppressive therapy. Strom *et al.* further disclose that the majority of basic protocols involve a combination of cyclosporine or Fk506 plus corticosteroids with or without azathioprine, and suggest that anti-lymphocyte globulin or OKT3 might also added to reduce the dose of cyclosporine required (page 454). Thus, while Strom *et al.* do include rapamycin in their general description of immunosuppressants, they do not actually teach or suggest the use of rapamycin in any multi-tiered immunosuppressive therapy regimen.

In short, none of the cited references alone or in combination suggest the use of a combination of rapamycin with at least two B7 antibodies as presently claimed. At best, the cited references might be viewed as providing the suggestion to try various combinations of immunosuppressive antibodies and immunosuppressive agents.

Indeed, Appellants respectfully submit that the Examiner has failed to point to any teaching in the Co. *et al.*, DeBoer, *et al.* and/or Cottens, *et al.* and Strom, *et al.* references that would compel one of ordinary skill in the art to make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and [b]oth the suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

With regard to the necessary legal standard for combining references, Applicants refer to *Arkie Lures v. Larew Tackle*, 119 F.3d 953 (Fed. Cir. 1997). In Arkie Lures, the Larew invention was directed to a "salt-impregnated fishing lure." In that case, the CAFC overturned the district court's finding of obviousness. The CAFC agreed that "[t]he use of salty bait to catch fish was known,[and] plastisol lures were known." *Id* at page 956. However, the CAFC found that although the literature on "fishing lures is apparently quite extensive, but despite the long use of salty lures and plastic lures, no reference was cited that showed or suggested this combination." The CAFC continued that "[t]he evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics." Id at page 957. The court further stated that:

> No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. . . . The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to do so in light of all the relevant factors. . . ***.It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements***. Indeed, the years of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination (emphasis added).

Id at pages 957 and 958.

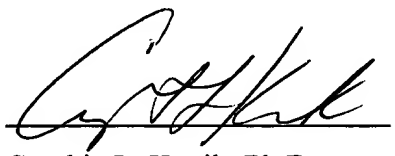
Similar to the situation in the *Arkie Lures* case, it is Applicants' position that despite the fact that the prior art contained the separate elements for downmodulating an immune response using the agents which inhibit a costimulatory signal and immunosuppressive agents, these individual teachings are insufficient to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention.

It is Applicants' position that, as in *In re Vaeck*, there is no teaching, either explicit or implicit, in any of the references cited by the Examiner which would have impelled one of ordinary skill in the art to make the instantly claimed invention. Given the standard for obviousness set forth by the CAFC, it is Applicants' position that the Examiner has improperly relied on hindsight obtained from Applicants' invention in making the combination of references cited.

SUMMARY

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. It there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicant's attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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